| Notice of Allowability | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/591,482 | MULLER ET AL. | |
| | Examiner | Art Unit | |
| | David S. Romeo | 1647 | |

***-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--***

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *12/2/9*.

2. ☒ The allowed claim(s) is/are *1,3-6,17,18,20,21,23,24,26,29,31-37 and 39*.

3. ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☒ All b) ☐ Some* c) ☐ None of the:
      1. ☒ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
**THIS THREE-MONTH PERIOD IS NOT EXTENDABLE**.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS ( as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review ( PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   **Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).**

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

**Attachment(s)**

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 1209
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☒ Interview Summary (PTO-413), Paper No./Mail Date *3/12/10* .
7. ☒ Examiner's Amendment/Comment
8. ☐ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

/David S Romeo/
Primary Examiner, Art Unit 1647

## EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Jennifer K. Holmes on 03/11/2010.

The application has been amended as follows:

IN THE SPECIFICATION:

On page 22, replace the Fig 6. legend with the following legend:

FIG. 6 shows an alignment of BMP-2 like proteins (SEQ ID NOs: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19 and 21) which upon exchanging the amino acid residue at the position corresponding to amino acid position 51 of human BMP-2 from leucine to preferably proline form preferred embodiments of the muteins according to the present invention;

IN THE CLAIMS:

1. A mutein of a bone morphogenetic protein, whereby the mutein consist of an amino acid substitution compared to the wild type of the bone morphogenetic protein, whereby the leucine in the wild type of the bone morphogenetic protein at the

amino acid position corresponding to amino acid position 51 of human BMP-2 is proline in the mutein.

2. (Cancelled)

3. The mutein according to claim 1, whereby the bone morphogenetic protein is selected from the group consisting of hBMP-2, hBMP-4, hBMP-5, hBMP-6, hBMP-7, hBMP-8, hGDF-5, mGDF-6, mGDF-7, hBMP-10 and hGDF-2.

4. The mutein according to claim 3, whereby

- the bone morphogenetic protein is hBMP-2 and the position corresponding to amino acid position 51 of human BMP-2 is amino acid position 51;

- the bone morphogenetic protein is hBMP-4 and the position corresponding to amino acid position 51 of human BMP-2 is amino acid position 53;

- the bone morphogenetic protein is hBMP-5 and the position corresponding to amino acid position 51 of human BMP-2 is amino acid position 68;

- the bone morphogenetic protein is hBMP-6 and the position corresponding to amino acid position 51 of human BMP-2 is amino acid position 68;

- the bone morphogenetic protein is hBMP-7 and the position corresponding to amino acid position 51 of human BMP-2 is amino acid position 75;

- the bone morphogenetic protein is hBMP-8 and the position corresponding to amino acid position 51 of human BMP-2 is amino acid position 75;

- the bone morphogenetic protein is hGDF-5 and the position corresponding to amino acid position 51 of human BMP-2 is amino acid position 56;

- the bone morphogenetic protein is mGDF-6 and the position corresponding to amino acid position 51 of human BMP-2 is amino acid position 56;

- the bone morphogenetic protein is mGDF-7 and the position corresponding to amino acid position 51 of human BMP-2 is amino acid position 82;

- the bone morphogenetic protein is hBMP-10 and the position corresponding to amino acid position 51 of human BMP-2 is amino acid position 44; and

- the bone morphogenetic protein is hGDF-2 and the position corresponding to amino acid position 51 of human BMP-2 is amino acid position 45.

5. The mutein according to claim 4, wherein the wild type of

- hBMP-2 comprises the amino acid sequence according to SEQ ID NO: 1;

- hBMP-4 comprises the amino acid sequence according to SEQ ID NO: 3;

- hBMP-5 comprises the amino acid sequence according to SEQ ID NO: 5;

- hBMP-6 comprises the amino acid sequence according to SEQ ID NO: 7;

- hBMP-7 comprises the amino acid sequence according to SEQ ID NO: 9;

- hBMP-8 comprises the amino acid sequence according to SEQ ID NO: 11;

- hGDF-5 comprises the amino acid sequence according to SEQ ID NO: 13;

- mGDF-6 comprises the amino acid sequence according to SEQ ID NO: 15;

- mGDF-7 comprises the amino acid sequence according to SEQ ID NO: 17;

- hBMP-10 comprises the amino acid sequence according to SEQ ID NO: 19; and

- hGDF-2 comprises the amino acid sequence according to SEQ ID NO: 21.

6. The mutein according to claim 5, whereby the wild type of

- hBMP-2 is encoded by a nucleic acid according to SEQ ID NO: 2;

- hBMP-4 is encoded by a nucleic acid according to SEQ ID NO: 4;

- hBMP-5 is encoded by a nucleic acid according to SEQ ID NO: 6;

- hBMP-6 is encoded by a nucleic acid according to SEQ ID NO: 8;

- hBMP-7 is encoded by a nucleic acid according to SEQ ID NO: 10;

- hBMP-8 is encoded by a nucleic acid according to SEQ ID NO: 12;

- hGDF-5 is encoded by a nucleic acid according to SEQ ID NO: 14;

- mGDF-6 is encoded by a nucleic acid according to SEQ ID NO: 16;

- mGDF-7 is encoded by a nucleic acid according to SEQ ID NO: 18;

- hBMP-10 is encoded by a nucleic acid according to SEQ ID NO: 20; and

- hGDF-2 is encoded by a nucleic acid according to SEQ ID NO: 22.

7. (Cancelled)

8. (Cancelled)

9. (Cancelled)

10. (Cancelled)

11. (Cancelled)

12. (Cancelled)

13. (Cancelled)

14. (Cancelled)

15. (Cancelled)

16. (Cancelled)

17. The bone morphogenetic mutein according to claim 1, whereby the bone morphogenetic protein is BMP-2 or pro-BMP-2.

18. A bone morphogenetic protein comprising the amino acid sequence according to any of SEQ ID NOs: 23 to 33.

19. (Cancelled)

20. A nucleic acid coding for a bone morphogenetic mutein according to claim 1 and/or the complement thereof.

21. The nucleic acid according to claim 20, wherein the nucleic acid comprises the nucleic acid sequence according to SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20 or 22, and/or the complement thereof.

22. (Cancelled)

23. A vector comprising a nucleic acid according to claim 20.

24. A cell comprising a nucleic acid according to claim 20.

25. (Cancelled)

26. A method for the production of a bone morphogenetic mutein, comprising the steps of

a) cultivating a cell according to claim 24 in a cultivation broth and

b) preparing the bone morphogenetic mutein from the cell and/or from the cultivation broth.

27. (Cancelled)

28. A composition comprising a mutein according to claim 1 and a pharmaceutically acceptable carrier.

29. A composition comprising a nucleic acid according to claim 20, and a pharmaceutically acceptable carrier.

30. (Cancelled)

31. A method for the treatment of a disease selected from the group consisting of fibrotic diseases, wound healing, hypervascularization, vascular diseases, fractures, and osteoporosis comprising administering to a patient in need of such treatment a mutein of a bone morphogenetic protein, whereby the mutein consist of an amino acid substitution compared to the wild type of the bone morphogenetic protein, whereby the leucine in the wild type of the bone morphogenetic protein at the amino acid position corresponding to amino acid position 51 of human BMP-2 is substituted, whereby the mutein binds to a BMP antagonist selected from the group consisting of the noggin protein family, the DAN protein family and the chordin protein family, whereby the mutein does not bind to BMP receptor BRIA or BRIB.

32. The method according to claim 31, whereby the fibrotic disease is selected from the group consisting of renal fibrosis, hepatic cirrhosis, pulmonary fibrosis and chronic inflammation.

33. The method according to claim 31, wherein the wound healing is associated with keloid, cicatrization, or peritoneal obliteration.

34. The method according to claim 31, whereby the hypervascularization is associated with retinopathies, arteriosclerosis and/or tumors.

35. The method according to claim 31, whereby the fractures are non-healing fractures.

36. The method according to claim 31, whereby the disease is osteoporosis.

37. A method for inhibiting a BMP antagonist selected from the group consisting of the noggin protein family, the DAN protein family and the chordin protein family, comprising administering to a patient a bone morphogenetic mutein according to claim 1.

38. (Cancelled)

39. The method according to 31, whereby the leucine in the wild type of the bone morphogenetic protein at the amino acid position corresponding to amino acid position 51 of human BMP-2 is substituted to proline.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (571) 272-0890. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 9:00 A.M. TO 5:30 P.M. IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, GARY NICKOL, CAN BE REACHED AT (571)272-0939.

IF SUBMITTING OFFICIAL CORRESPONDENCE BY FAX, APPLICANTS ARE ENCOURAGED TO SUBMIT OFFICIAL CORRESPONDENCE TO THE CENTRAL FAX NUMBER FOR OFFICIAL CORRESPONDENCE, WHICH IS (571) 273-0835.

CUSTOMERS ARE ALSO ADVISED TO USE CERTIFICATE OF FACSIMILE PROCEDURES WHEN SUBMITTING A REPLY TO A NON-FINAL OR FINAL OFFICE ACTION BY FACSIMILE (SEE 37 CFR 1.6 AND 1.8).

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING MAY BE OBTAINED FROM THE PATENT APPLICATION INFORMATION RETRIEVAL (PAIR) SYSTEM. STATUS INFORMATION FOR PUBLISHED APPLICATIONS MAY BE OBTAINED FROM EITHER PRIVATE PAIR OR PUBLIC PAIR. STATUS INFORMATION FOR UNPUBLISHED APPLICATIONS IS AVAILABLE THROUGH PRIVATE PAIR ONLY. FOR MORE INFORMATION ABOUT THE PAIR SYSTEM, SEE HTTP://PAIR-DIRECT.USPTO.GOV. CONTACT THE ELECTRONIC BUSINESS CENTER (EBC) AT 866-217-9197 (TOLL-FREE) FOR QUESTIONS ON ACCESS TO THE PRIVATE PAIR SYSTEM,

/DAVID S ROMEO/
PRIMARY EXAMINER, ART UNIT 1647

DSR
MARCH 12, 2010